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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>4</sup> :</b> <b>A61K 31/56</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 87/ 07141</b> <b>(43) International Publication Date:</b> 3 December 1987 (03.12.87)
<b>(21) International Application Number:</b> PCT/US86/01862 <b>(22) International Filing Date:</b> 10 September 1986 (10.09.86) <b>(31) Priority Application Number:</b> 866,605 <b>(32) Priority Date:</b> 23 May 1986 (23.05.86) <b>(33) Priority Country:</b> US  <b>(71) Applicant:</b> NEW ENGLAND MEDICAL CENTER HOSPITALS, INC. [US/US]; 171 Harrison Avenue, Boston, MA 02111 (US). <b>(72) Inventor:</b> SCHWARTZ, Bernard ; 180 Beacon Street, Boston, MA 02116 (US). <b>(74) Agent:</b> KENWAY & JENNEY; 60 State Street, Boston, MA 02109 (US).		<b>(81) Designated States:</b> AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).  <b>Published</b> <i>With international search report.</i> <i>With amended claims.</i>
<b>(54) Title:</b> METHOD FOR TREATING GLAUCOMA  <b>(57) Abstract</b>  A method for treating glaucoma consisting of exposing the eye to a corticosteroid and then applying an adrenergic agent to the eye which acts to decrease ocular pressure. Useful adrenergic agents include both alpha and beta agonists and antagonists, including, for example, epinephrine, dipivalyl epinephrine, betaxolol, levobunolol and timolol. Useful steroids, which are preferably applied topically, include dexamethasone, prednisone, cortisone, and triamcinolone. In the preferred embodiment, a solution of less than 0.1 % dexamethasone and a solution of less than 2 % epinephrine or less than 0.1 % dipivalyl epinephrine are topically applied to the eye.		

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-1-

METHOD FOR TREATING GLAUCOMABackground of the Invention

This invention is in the field of treatments of eye disease and more particularly in the area of treatments for glaucoma.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. The most common cause of glaucoma is restricted outflow of aqueous fluid from the anterior chamber of the eye through Schlemm's canal, the trabecular meshwork and the aqueous veins, shown in the diagram of the human eye in Fig. 1. Glaucoma, if untreated, can cause excavation and degeneration of the optic disc and nerve fiber bundle damage producing defects in the field of vision and eventually permanent blindness. Roughly two million Americans are afflicted, making glaucoma one of the leading causes of blindness in the United States.

Glaucoma may have a variety of causes, including hereditary predisposition, congenital malformation, disease, injury or adverse drug reaction. For example, angle-closure glaucoma occurs because the outflow of the aqueous humor is mechanically prevented by contact of the iris with the trabecular drainage meshwork and peripheral cornea. Capsular glaucoma occurs in association with the widespread deposition of degenerative substance on the lens capsule, ocular blood vessels, iris and ciliary body. Corticosteroid-induced glaucoma is due to a hereditary predisposition to increased intraocular

-2-

pressure after local instillation of corticosteroid-containing eyedrops. Other types of glaucoma include hypersecretion glaucoma due to the excessive formation of aqueous humor; malignant glaucoma due to forward displacement of the iris and lens, obliterating the anterior chamber; and open-angle glaucoma, in which the aqueous humor has free access to the trabecular meshwork.

Glaucoma is treated either surgically or with antiglaucomatous agents. Examples of antiglaucomatous agents include echothiophate iodide, pilocarpine, methazolamide, timolol, and epinephrine, dipivalyl epinephrine and other epinephrine salts. Echothiophate iodide is a long-acting cholinesterase inhibitor for topical use which enhances the effect of endogenously-liberated acetylcholine in parasympathetically innervated structures of the eye to increase outflow of the aqueous humor to decrease intraocular pressure. Pilocarpine is a topically applied alkaloid which acts as a parasympathomimetic agent. Methazolamide is a potent inhibitor of the enzyme carbonic anhydrase which is taken orally and acts to lower intraocular pressure by inhibiting carbonic anhydrase in the various tissues of the eye. Timolol maleate is a general beta-adrenergic receptor-blocking agent which is effective in decreasing intraocular pressure. Epinephrine bitartrate, (-)-3,4,-Dihydroxy-alpha-[(methylamino) methyl] benzyl alcohol (+) tartrate (1:1) salt, is an adrenergic agent which reduces intraocular pressure by reducing the rate of aqueous formation and increasing the outflow of aqueous humor from the eye.

-3-

Epinephrine is a very effective drug against glaucoma and deserves use as the initial medical treatment of mild cases as well as in addition to other medications when required for control of difficult cases. Clinical studies, reported in Ocular Pharmacology, at pages 275-290 by William H. Havener (The C.V. Mosby Co., St. Louis, 1983), of a number of sympathomimetic compounds showed that a 1% to 2% solution of levo-epinephrine often helps to control glaucoma.

For example, topical application of a 2% solution of levo-epinephrine to 44 glaucomatous eyes caused an average drop in pressure of 13.5 mm Hg, ranging from 3 to 38 mm Hg. A marked pressure drop was obtained within 1 hour, and pressure continued to fall slightly for 4 hours. A slow rise followed, with a good effect lasting for 12 hours and a slight effect for as long as 24 hours. Eyes most likely to respond well to a 2% solution of levo-epinephrine were those with a coefficient of outflow better than 0.15, the pressures of which were maintained in the upper twenties with miotics. The pressure in most of these eyes could be dropped to the low twenties or below by instillation of a 2% solution of levo-epinephrine twice daily. Although in some instances glaucoma could be controlled by a 2% concentration of levo-epinephrine alone, the best results were obtained when this drug was used in combination with a miotic such as pilocarpine.

It is desirable to use as low a concentration of epinephrine as possible since

-4-

epinephrine frequently causes side effects such as local allergy and systemic cardiovascular adrenergic responses and it may cause angle-closure glaucoma and aphakic maculopathy. A pressure-lowering effect can be demonstrated with epinephrine concentrations as low as 0.125%. However, a substantially greater response occurs with a 1% to 2% solution. Dipivalyl epinephrine is a lipophilic epinephrine derivative and is converted to epinephrine in the ocular tissue. It is reported to have fewer side effect than epinephrine (William H. Havener, Ocular Pharmacology at pages 287-289)

In general, drugs such as steroids are not used in the treatment of glaucoma. Rather, prolonged use of steroids such as dexamethasone sodium phosphate can result in elevated intraocular pressure, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation or secondary ocular infections. Further, viral, bacterial and fungal infections of the cornea may be exacerbated by the topical application of steroids to the eye.

Although the antiglaucomatous agents are generally effective in the treatment of glaucoma, they have both systemic and local side effects which may be serious in combination with other medical treatments such as anesthesia or the systemic use of other drugs. Beta blocker drugs such as timolol, betaxalol and levobunolol cannot be used with people suffering from asthma or heart problems.

-5-

Systemic effects of epinephrine include increased blood pressure, faintness, headaches, and interactions with anesthesia. The side effects of topical epinephrine include burning, slow wound healing, pigment deposition and eyelash loss. Early commercial preparations of levo-epinephrine produced a very severe burning sensation, which was often sufficiently marked to incapacitate the patient for a minute or so and required preliminary use of a local anesthetic in some patients. Presently available preparations still cause tearing, burning and ocular discomfort. Mitosis and migration of corneal epithelial cells is inhibited by epinephrine and the time required for healing of corneal epithelial defects is doubled. Prolonged topical use of levo-epinephrine occasionally causes a local conjunctival allergy and localized conjunctival deposits of pigment. Corneal pigmentation caused by epinephrine is particularly likely to occur in eyes with a damaged epithelium and is enhanced by the use of old and discolored solutions of oxidized epinephrine. Topical epinephrine therapy can also cause plastic artificial eyes and contact lenses to turn black.

The side effects of topical epinephrine therapy are quite annoying. In one series of 50 patients, reported in Ocular Pharmacology by William H. Havener at pages 275-290, only 20% could continue epinephrine drops for a four-year period. Reactive hyperemia, irritation, and tearing affected two-thirds of the patients. Headaches affected 5 patients; cardiac palpitations, 4; blurred vision, 10; allergy, 6; and conjunctival pigmentation, 12.

-6-

It is therefore an object of the present invention to provide a method of treatment of glaucoma which is safe, effective, and has a minimum of side effects.

It is a further object of the present invention to provide a method of treatment of glaucoma which utilizes a minimum of biologically-active compounds.

It is a still further object of the present invention to provide a method for treatment of glaucoma which produces a decrease in ocular pressure which is of a reasonable duration.

#### Summary of the Invention

The present invention is a method for treating glaucoma in humans which consists of topically applying to the eye two drugs: a corticosteroid and an adrenergic agent, including alpha and beta agonists and antagonists. The preferred drugs are dexamethasone and epinephrine or dipivalyl epinephrine. The treatment results in a decrease in intraocular pressure.

In the preferred embodiment, a solution of less than 0.1% dexamethasone is topically applied to the eye followed by topical application of a solution of less than 2% epinephrine or 0.1% dipivalyl epinephrine. At concentrations of 0.1% or more, prolonged use of dexamethasone can produce increased intraocular pressure. The interaction of the two drugs is important in determining the extent and

-7-

duration of decrease of intraocular pressure, as shown by dose response curves relating intraocular pressure to the concentrations of the dexamethasone and epinephrine. The two drugs may be topically applied in combination or in sequence. The corticosteroid may also be given orally although this is not the preferred route of administration.

The effectiveness of the combination of dexamethasone and epinephrine is unexpected since both systemic and topical application of dexamethasone or other corticosteroid tends to increase ocular pressure. Observations have been made in both rabbits and humans demonstrating the effectiveness of the combination.

#### Brief Description of the Drawings

Fig. 1 is a cross-sectional view of the right human eye.

Fig. 2 is a graph of intraocular pressure response (mm Hg) to 0.1% epinephrine bitartrate, with and without 0.1% dexamethasone.

Fig. 3 is a graph of the dose response for concentrations of epinephrine bitartrate from 0.05% to 2% as measured by the difference in mean intraocular pressure (epinephrine minus dexamethasone/epinephrine) at 45 minutes after treatment with epinephrine.

Fig. 4 is a graph of the average maximum decrease in ocular pressure from untreated pressure (mm Hg) following application of 0.1% dexamethasone in

-8-

combination with epinephrine at a concentration between 0.001% and 0.1%.

Fig. 5 is a graph of the effect of varying doses of epinephrine and dexamethasone on the average decrease of ocular pressure up to the maximum pressure difference, expressed as the difference between dexamethasone plus epinephrine minus epinephrine alone, compared to the average pressure prior to epinephrine application.

Fig. 6 is a graph of the duration of the effect on ocular pressure of treatment with dexamethasone at a concentration between 0.001% and 0.1% combined with epinephrine at a concentration between 0.001% and 0.1% versus epinephrine alone at a concentration between 0.001% and 0.1%.

#### Detailed Description of the Invention

The present invention is the treatment of glaucoma with two drugs: a corticosteroid such as dexamethasone and an adrenergic agent.

A number of adrenergic agents are useful in the present invention, including both alpha and beta agonists such as epinephrine, dipivalyl epinephrine and other epinephrine salts, and alpha and beta antagonists such as timolol, butaxolol, levobunolol, and various combinations of these drugs.

Epinephrine bitartrate is a standard drug used in the treatment of glaucoma. Epinephrine reduces the rate of aqueous humor formation and

-9-

improves the facility of outflow of aqueous humor. This improved facility is not immediate but may be observed after several months of topical epinephrine therapy. Epinephrine and dipivalyl epinephrine are useful in the management of chronic simple (open-angle) glaucoma, either alone or in combination with miotics such as pilocarpine, carbonic anhydrase inhibitors, or beta receptor blockers such as timolol. When applied in the absence of corticosteroids, in the conventional manner, epinephrine is topically applied as a sterile aqueous 2% solution on an individual basis, ranging from twice daily to once every two or three days. More frequent instillation than one drop four times daily does not usually elicit any further improvement in therapeutic response. Dipivalyl epinephrine is conventionally applied as a 0.1% solution. Betaxolol and levobunolol are typically applied as a 0.5% solution. Timolol is applied as a 0.25 or 0.5% solution. In the present invention, lower concentrations are used due to the enhancing effect of the corticosteroid. This has the advantage of decreasing the incidence or severity of side effects due to the adrenergic agent.

Examples of corticosteroids which are useful in the present invention include dexamethasone, prednisone, prednisolone, hydrocortisone, cortisone, fludrocortisone, betamethasone, methyl prednisone, triamcinolone, and their derivatives.

Dexamethasone sodium phosphate and other corticosteroids are conventionally used for the treatment of steroid-responsive inflammatory

-10-

conditions such as allergic conjunctivitis, superficial punctate keratitis, herpes zoster keratitis, corneal injury from chemical or thermal burns, and in other situations where an inflammatory response has been incited by mechanical, chemical or immunological agents. In general, one or two drops of a 0.1% dexamethasone phosphate solution are topically applied to the eye between three and four times a day up to once every hour, depending on the treatment required. Prolonged use must be avoided as the dexamethasone causes increased ocular pressure over time. People on systemic corticosteroids frequently also exhibit increased ocular pressures. In the present invention, the dosage of the corticosteroid is individually adjusted as necessary to produce the desired enhancement of pressure decrease, due to the adrenergic agent, which is also of sufficient duration. In general, very small concentrations of corticosteroids will be required.

Medications are routinely applied to the eye by means of a dropper. Variations in the actual amount delivered to the eye will vary somewhat according to the shape and size of the dropper and the skill of the person administering the drops.

In combination with epinephrine, dexamethasone has been demonstrated to enhance the effectiveness of epinephrine in decreasing intraocular pressure, allowing the use of lower concentrations of epinephrine to achieve the same decrease in pressure. Since the mechanism by which this occurs involves an enhancement in the number, binding affinity, or some

-11-

other function of the adrenergic receptors by the corticosteroids, other corticosteroids may be used with other adrenergic agents to produce the same result. The advantages are immediately noticeable, most significant being the decrease in both systemic and local side effects due to the adrenergic agent.

The preferred treatment of glaucoma according to the present invention is to pretreat the eye with a solution of less than 0.1% dexamethasone followed by topical application of a less than 2% solution of epinephrine or a less than 0.1% solution of dipivalyl epinephrine. The decrease of intraocular pressure is a function of the interaction of the two drugs. They may be applied in combination or in sequence.

This invention is further illustrated by the following non-limiting examples. In the first group of examples, rabbit eyes were treated with a combination of dexamethasone and epinephrine to decrease ocular pressure. Rabbits are the standard model for testing the reaction of human eyes to drugs or other foreign agents. In the second group of examples, clinical observations were made on patients suffering from elevated ocular pressures.

Example 1: Effect of dexamethasone on  
epinephrine-induced decrease in  
ocular pressure in rabbits.

New Zealand white rabbits were used in a study to measure pressure changes as a function of

-12-

dexamethasone in combination with epinephrine. The rabbits were acclimated to their new surroundings and frequent handling, including the measurement of intraocular pressure, by having serial intraocular pressure measurements taken daily for four to seven days prior to the beginning of the testing. The experiment was begun only when these daily pressure readings were stable. The intraocular pressure was measured with a Digilab (Cambridge, Massachusetts) pneumatonometer after application of 0.05% proparacaine (Alcaine) for corneal anesthesia.

Rabbits were randomized into four groups: a first control group receiving saline placebo drops in both eyes; a second epinephrine group treated with placebo followed by epinephrine bitartrate solution; a third dexamethasone/ epinephrine group receiving a pretreatment with dexamethasone phosphate followed by epinephrine; and a fourth group serving as a second control group, receiving only 0.1% dexamethasone in both eyes.

The rabbits' eyes were pretreated with five applications of a single drop of placebo saline or dexamethasone, depending on the protocol of the assigned group. The pretreatment was followed by treatment with placebo or epinephrine. Baseline intraocular pressures were measured at 8:00 a.m., 8:30 a.m., and 9:00 a.m. Placebo or dexamethasone phosphate was administered every 15 minutes from 9:15 a.m. to 10:15 a.m., for a total of five applications. Intraocular pressure was measured again at 10:30 a.m. At 10:45 a.m., the animals were treated with one drop

-13-

of either placebo or epinephrine bitartrate topically, and intraocular pressure was subsequently measured about every 30 minutes until 3:00 p.m.

Depending on the experiment, concentrations of epinephrine bitartrate used were between 0.001% and 2%. Dexamethasone phosphate was used at concentrations between 0.001% and 0.1%. Both the epinephrine and dexamethasone solutions were prepared at the time of each experiment by dissolving the solute in 0.9% saline solution. The placebo drops were 0.9% saline solution.

Each experiment was carried out several times. The results are shown in Figure 2-6. Each time there were three animals in the control, epinephrine, and dexamethasone/epinephrine groups. The number of animals used in each group is noted on the Figures containing the results.

The Kruskal-Wallis test described in Nonparametric Statistics for the Behavioral Sciences by S. Siegel (McGraw-Hill, New York, 1956) was used for statistical analysis to detect differences in intraocular pressure between the groups. When the test demonstrated a significant difference, p value less than 0.05, occurring between two of the three test groups, Dunn's pairwise comparison, also described by S. Siegel, was used to detect statistically significant differences between the two groups. The statistical analysis of right and left eyes was performed separately.

-14-

The control animals showed little change in intraocular pressure, establishing that neither 0.1% dexamethasone alone nor saline had any effect on intraocular pressure. Both the epinephrine group and the dexamethasone/epinephrine groups demonstrated significant decreases in intraocular pressure when compared to the control groups. For the 2.0% and 0.5% epinephrine concentrations, however, there were no statistically significant differences between the two groups after the instillation of epinephrine, in spite of lower intraocular pressures in the dexamethasone/epinephrine group than in the epinephrine group. The results for the right and left eyes were similar.

In the first group of experiments, the decrease in intraocular pressure as a function of 0.1% epinephrine and as a function of 0.1% epinephrine in combination with 0.1% dexamethasone over a period of several hours was compared. The analysis of the data for the 0.1% epinephrine group, right eye, demonstrated a significant decrease in intraocular pressure in the dexamethasone/epinephrine group compared to the epinephrine group. The results for the left eyes treated with 0.1% epinephrine, shown in Fig. 2, demonstrated significant decreases in intraocular pressures in the dexamethasone/epinephrine group at 45 minutes and 75 minutes after epinephrine, with a marginally significant decrease noted at 15 minutes. The 0.5% epinephrine group demonstrated a borderline significant value for the left eye at 15 minutes after administration of epinephrine.

-15-

The second group of experiments compared the decrease in intraocular pressure as a function of epinephrine concentration in combination with 0.1% dexamethasone.

Fig. 3 plots the dose response to epinephrine, showing the difference in mean ocular pressure between treatment with dexamethasone/epinephrine and treatment with epinephrine alone at 45 minutes after topical epinephrine administration. The concentration of epinephrine ranged from 0.05 to 2%.

Fig. 4 is a graph showing the average maximum decrease in pressure in relation to pre-epinephrine pressures obtained using 0.1% dexamethasone with varying concentrations of epinephrine, ranging from 0.001 to 0.1%. There is an effect at as low of a concentration as 0.001% epinephrine. However, the effect appears to peak at about 0.01% epinephrine.

Test results obtained using 0.01% dexamethasone were comparable to those obtained with 0.1% dexamethasone, as shown in Fig. 5 comparing the average decrease in pressure for 0.1% dexamethasone in combination with epinephrine at a concentration ranging from 0.001% up to 0.1% (left) with the average decrease in pressure for 0.01% dexamethasone and 0.01% dexamethasone in combination with 0.01% epinephrine (right). The pressure decrease was measured as follows. Five measurements were taken of the eye pressure. Dexamethasone was then applied to the eye,

-16-

followed by application of the epinephrine. The pressure was then measured and the average change in pressure between the initial pressure and the maximum decrease in pressure determined. Epinephrine alone was used as the control.

It is better to use a lower concentration of dexamethasone since long term use of 0.1% dexamethasone would otherwise negate the pressure decreasing effect of the epinephrine. 0.01% dexamethasone produces a decrease in ocular pressure of 5.5 mm Hg more than epinephrine alone does. With 0.001% dexamethasone, a decrease in pressure of 3.3 mm Hg more than is produced by epinephrine alone was obtained.

As one goes to the lower concentrations of dexamethasone, the duration of the effectiveness of the medication is altered. This is shown in Fig. 6 where the duration in minutes versus various concentrations of dexamethasone-epinephrine is graphed. On the left hand side of the plot, 0.1% dexamethasone was used in combination with epinephrine at a concentration between 0.001% and 0.1%. On the right hand side of the plot, 0.01% epinephrine was used with two different concentrations of dexamethasone, 0.01% and 0.001%. The duration in decrease of ocular pressure is greater for 0.1% dexamethasone in combination with 0.01% epinephrine than 0.01% dexamethasone in combination with 0.01% epinephrine (240 min. vs. 145 min.). The duration is slightly less with 0.001% dexamethasone in combination with 0.01% epinephrine than 0.01% dexamethasone in

-17-

combination with 0.01% epinephrine (137 min. vs. 145 min.). Both 0.001% dexamethasone and 0.01% dexamethasone in combination with 0.01% epinephrine produce a longer duration of decreased ocular pressure than 0.01% epinephrine alone (145 min. and 137 min. vs. 105 to 97 min.).

Part of the therapeutic effectiveness of treatment for glaucoma is to have an eyedrop that has a relatively long duration of effect so that the patient does not have to continuously place eyedrops. Duration is therefore an important consideration.

Example 2: Enhanced ocular pressure decrease in a patient on a systemic corticosteroid following topical application of epinephrine.

A 57 year old white female was first observed on March 27, 1985 for routine ocular examination. Ocular pressures were 21 mm Hg right eye and 23 mm Hg left eye. The patient had emphysema and treatment with 25 mg prednisone once a day was begun in December 1985. The patient was next seen on April 1, 1986. Ocular pressures were markedly increased, up to 44 mm Hg in the right eye and 52 mm Hg in the left eye. In view of the results in rabbits wherein corticosteroids enhanced the effect of epinephrine in lowering ocular pressure, the patient was begun on 2% epinephrine drops one twice a day in both eyes. The following day, April 2, 1986, ocular pressure had decreased to 24 mm Hg right eye and 26 mm Hg left eye. One week later, when the patient was last seen on the

-18-

same medication, the ocular pressures were 17 mm Hg in the right eye and 16 mm Hg in the left eye.

The patient showed a dramatic decrease in ocular pressure in response to 2% epinephrine, twice or more as large as would be expected with 2% epinephrine. The enhanced effect presumably was due to the systemic prednisone therapy.

Example 3: Enhanced ocular pressure decrease in a patient on a systemic corticosteroid following topical application of epinephrine in combination with timolol.

A 67 year old white male with hemolytic anemia was first seen on July 8, 1982 for ocular examination. He had been on prednisone for the past 19 years in doses ranging from 10 mg to 80 mg per day.

On ocular examination, ocular pressures were 59 mm Hg in the right eye and 40 mm Hg in the left eye. He was placed on 0.25% timolol drops, one twice a day in both eyes.

The following day, July 9, 1982, his ocular pressures were 28 mm Hg in the right eye and 20 mm Hg in the left eye. Subsequently he was placed on 0.5% timolol drops, one twice a day in both eyes to replace 0.25% timolol drops, with a decrease in ocular pressure to 24 mm Hg in the right eye and 16 mm Hg in the left eye. To produce a further decrease in ocular pressures, 2% epinephrine drops were added twice a day to both eyes. Ocular pressure on November 9, 1982

-19-

with the above therapy were 18 mm Hg right eye and 16 mm Hg left eye.

This case demonstrates that timolol drops have an enhanced effect in lowering ocular pressures 31 mm Hg in the right eye and 20 mm Hg in the left eye in a patient who had been on steroid therapy. This is larger than one would expect for the pressure lowering effect of timolol drops in patients who are not on steroid therapy. This case also shows that when epinephrine drops were added, the combination of epinephrine drops and timolol drops in a patient on steroid therapy were effective in normalizing the ocular pressure.

Although the present invention has been described with reference to its preferred embodiment, variations and modifications of the method of the present invention will be obvious to those skilled in the art, and it is intended that all such modifications and variations be included within the scope of the appended claims.

I claim:

-20-

1. A method for treating eye defects or disease characterized by elevated intraocular pressure comprising

exposing the eye to a corticosteroid and applying an adrenergic agent to the eye, wherein said corticosteroid and said adrenergic agent act in cooperation to decrease the intraocular pressure.

2. The method of claim 1 further comprising selecting the concentration of the adrenergic agent to be less than the effective concentration of the adrenergic agent in the absence of the corticosteroid.

3. The method of claim 1 further comprising selecting the adrenergic agent from the group consisting of alpha agonists, beta agonists, alpha antagonists, beta antagonists, and combinations thereof.

4. The method of claim 3 further comprising selecting the adrenergic agent from the group consisting of solutions of less than 2% epinephrine, 0.1% dipivalyl epinephrine, 0.5% betaxolol, 0.5% levobunolol, 0.5% timolol, and combinations thereof.

5. The method of claim 1 further comprising selecting the corticosteroid from the group consisting of dexamethasone, prednisone, prednisolone, hydrocortisone, cortisone, fludrocortisone, beta methasone, methyl prednisone, triamcinolone, and derivatives and combinations thereof.

-21-

6. The method of claim 5 wherein the corticosteroid is a solution of less than 0.1% dexamethasone.

7. The method of claim 1 wherein the corticosteroid and the adrenergic agent are topically applied in combination.

8. The method of claim 1 wherein the corticosteroid is administered systemically.

9. A solution for treating glaucoma comprising:

a corticosteroid and  
an adrenergic agent,  
wherein said corticosteroid and said adrenergic agent act in cooperation to decrease intraocular pressure.

10. The solution of claim 9 wherein the adrenergic agent is selected from the group consisting of alpha agonists, beta agonists, alpha antagonists, beta antagonists, and combinations thereof.

11. The solution of claim 10 wherein the adrenergic agent is selected from the group consisting of solutions of less than 2% epinephrine, 0.1% dipivalyl epinephrine, 0.5% betaxolol, 0.5% levobunolol, 0.5% timolol, and combinations and derivatives thereof.

12. The solution of claim 9 wherein the corticosteroid is a solution of less than 0.1% dexamethasone.

-22-

13. The solution of claim 9 wherein the corticosteroid is a solution of less than 0.1% dexamethasone and the adrenergic agent is selected from the group consisting of solutions of less than 2% epinephrine, 0.1% dipivalyl, 0.5% betaxolol, 0.5% levobunolol, 0.5% timolol, and combinations thereof.

## AMENDED CLAIMS

[received by the International Bureau on 30 December 1986(30.12.86);  
original claims 1 - 9 amended; remaining claims unchanged (3 pages) ]

1. A method for treating eye defects or disease characterized by elevated intraocular pressure comprising selecting a corticosteroid and an adrenergic agent, wherein said corticosteroid and said adrenergic agent act in cooperation to decrease intraocular pressure and the concentrations of said corticosteroid and said adrenergic agent are selected to produce a prolonged decrease in intraocular pressure when the eye is exposed to said corticosteroid and said adrenergic agent in combination.
2. The method of claim 1 further comprising selecting the concentration of the adrenergic agent to be less than the effective concentration of the adrenergic agent in the absence of the corticosteroid.
3. The method of claim 1 further comprising selecting the adrenergic agent from the group consisting of alpha agonists, beta agonists, alpha antagonists, beta antagonists, and combinations thereof.
4. The method of claim 3 further comprising selecting the adrenergic agent from the group consisting of solutions of less than 2% epinephrine, 0.1% dipivalyl epinephrine, 0.5% betaxolol, 0.5% levobunolol, 0.5% timolol, and combinations thereof.
5. The method of claim 1 further comprising selecting the corticosteroid from the group consisting of dexamethasone, prednisone, prednisolone, hydrocortisone, cortisone, fludrocortisone, beta methasone, methyl prednisone, triamcinolone, and derivatives and combinations thereof.
6. The method of claim 5 wherein the corticosteroid is a solution of less than 0.1% dexamethasone.

7. The method of claim 1 wherein the corticosteroid and the adrenergic agent are topically applied in combination.

8. The method of claim 1 wherein the corticosteroid is administered systemically.

9. A solution for treating glaucoma comprising:  
a corticosteroid and  
an adrenergic agent,  
wherein said corticosteroid and said adrenergic agent act in cooperation to decrease intraocular pressure and the concentrations of said corticosteroid and said adrenergic agent are selected to produce a prolonged decrease in intraocular pressure when the eye is exposed to said corticosteroid and said adrenergic agent in combination.

10. The solution of claim 9 wherein the adrenergic agent is selected from the group consisting of alpha agonists, beta agonists, alpha antagonists, beta antagonists, and combinations thereof.

11. The solution of claim 10 wherein the adrenergic agent is selected from the group consisting of solutions of less than 2% epinephrine, 0.1% dipivalyl epinephrine, 0.5% betaxolol, 0.5% levobunolol, 0.5% timolol, and combinations and derivatives thereof.

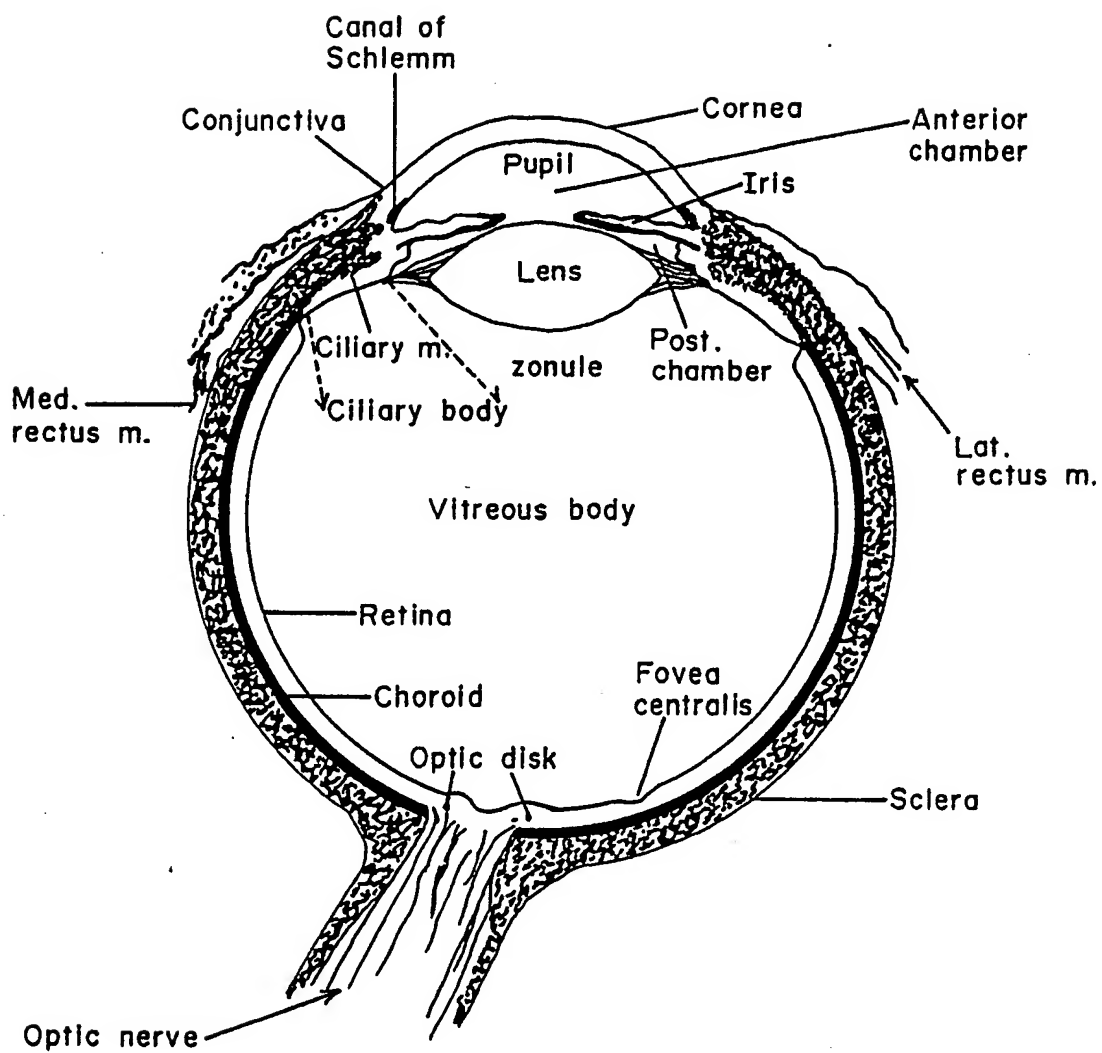
12. The solution of claim 9 wherein the corticosteroid is a solution of less than 0.1% dexamethasone.

13. The solution of claim 9 wherein the corticosteroid is a solution of less than 0.1% dexamethasone and the adrenergic agent is selected from the group consisting of solutions of less

than 2% epinephrine, 0.1% dipivalyl, 0.5% betaxolol, 0.5% levobunolol, 0.5% timolol, and combinations thereof.

1/6

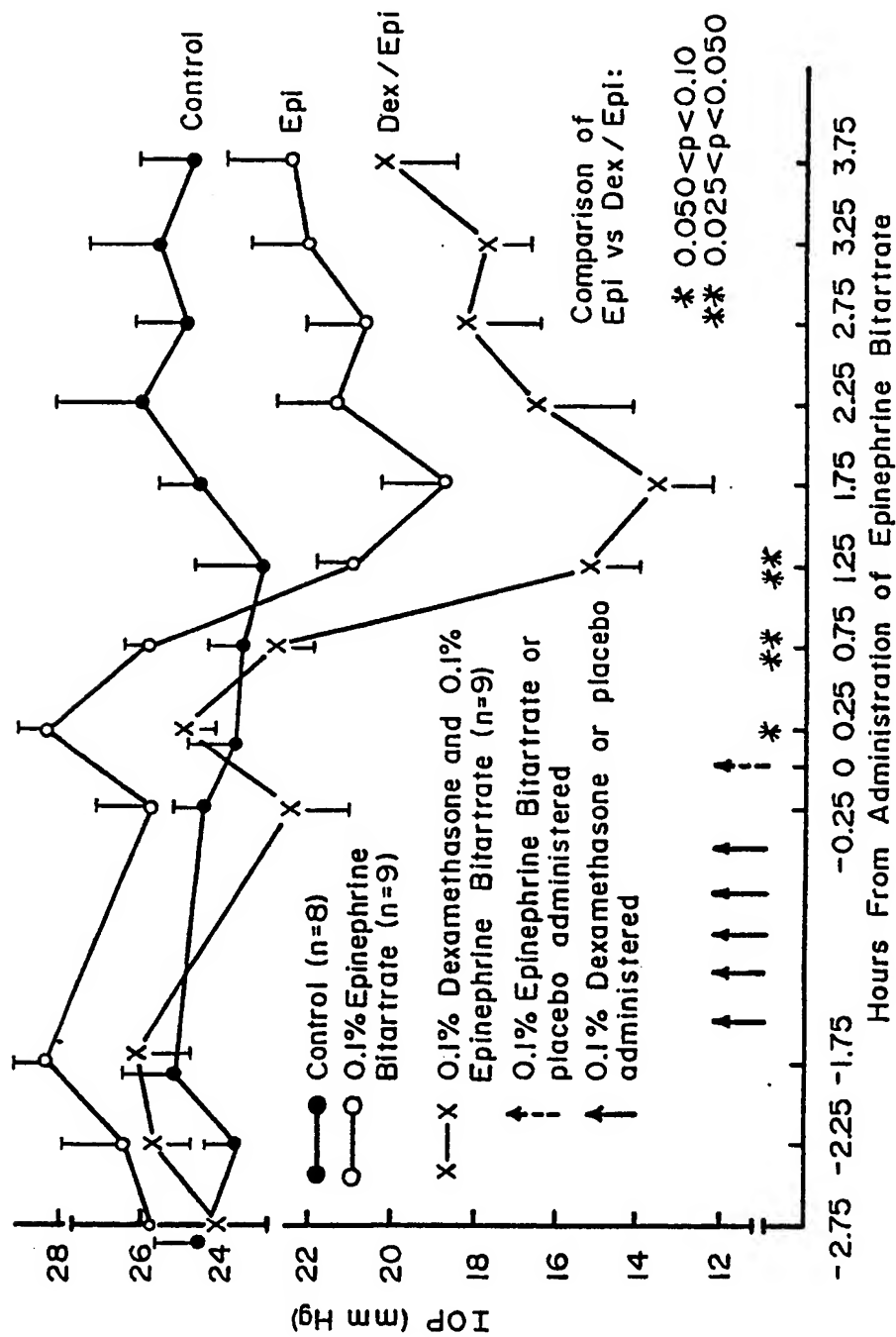
FIGURE 1



The Human Eye (Right)

2/6

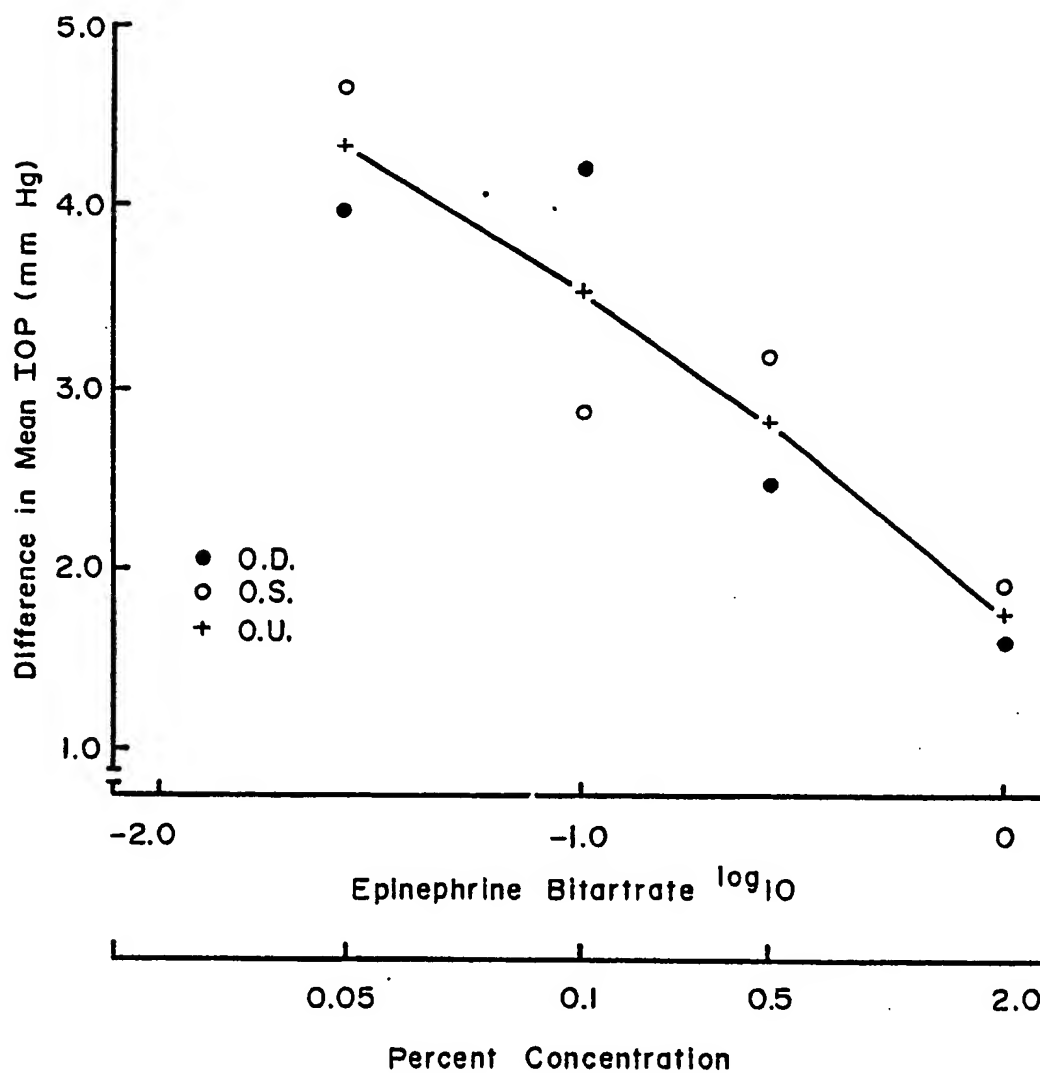
FIGURE 2  
IOP RESPONSE TO 0.1% EPINEPHRINE BITARTRATE  
(MEAN  $\pm$  S.E.M.)  
O.S.



3/6

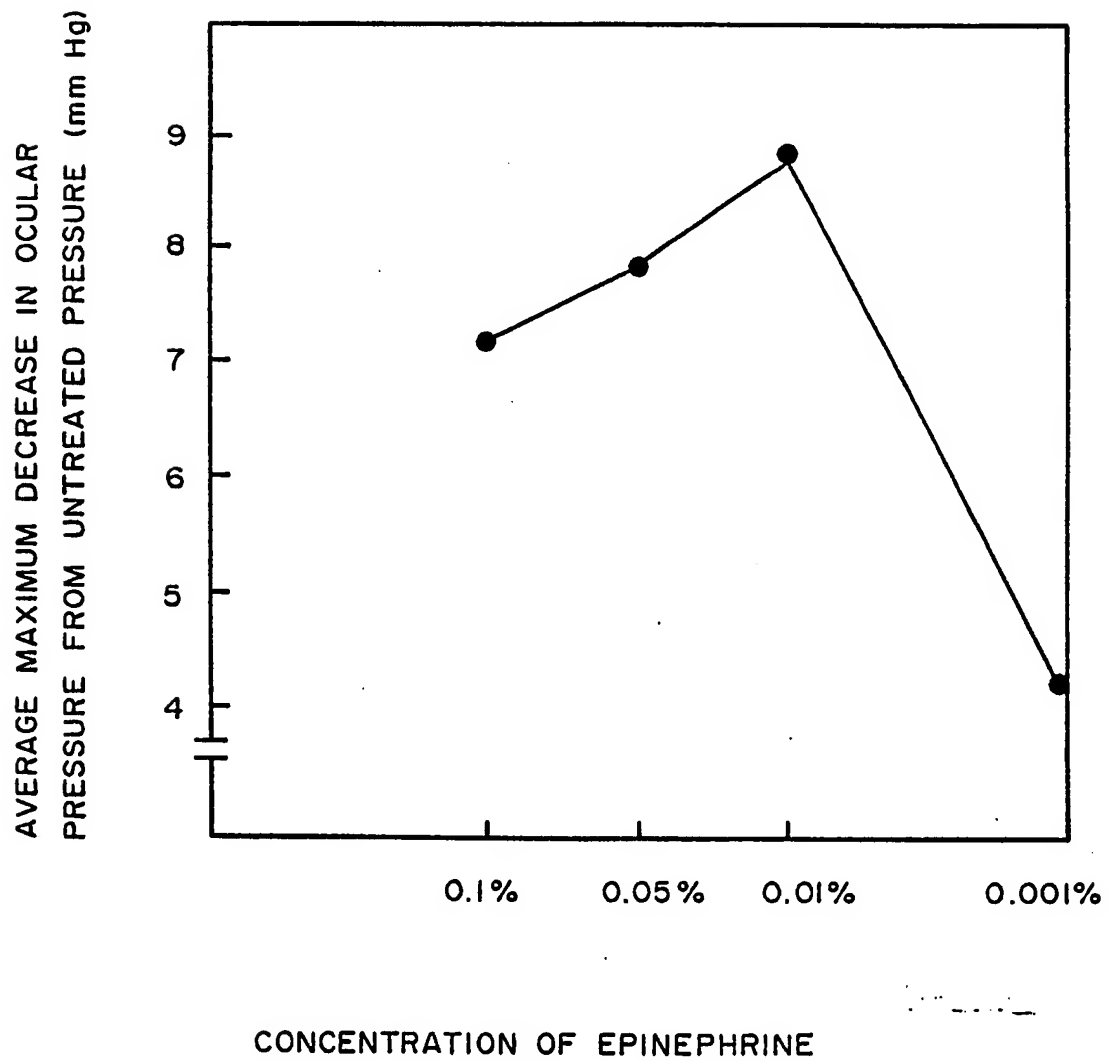
FIGURE 3

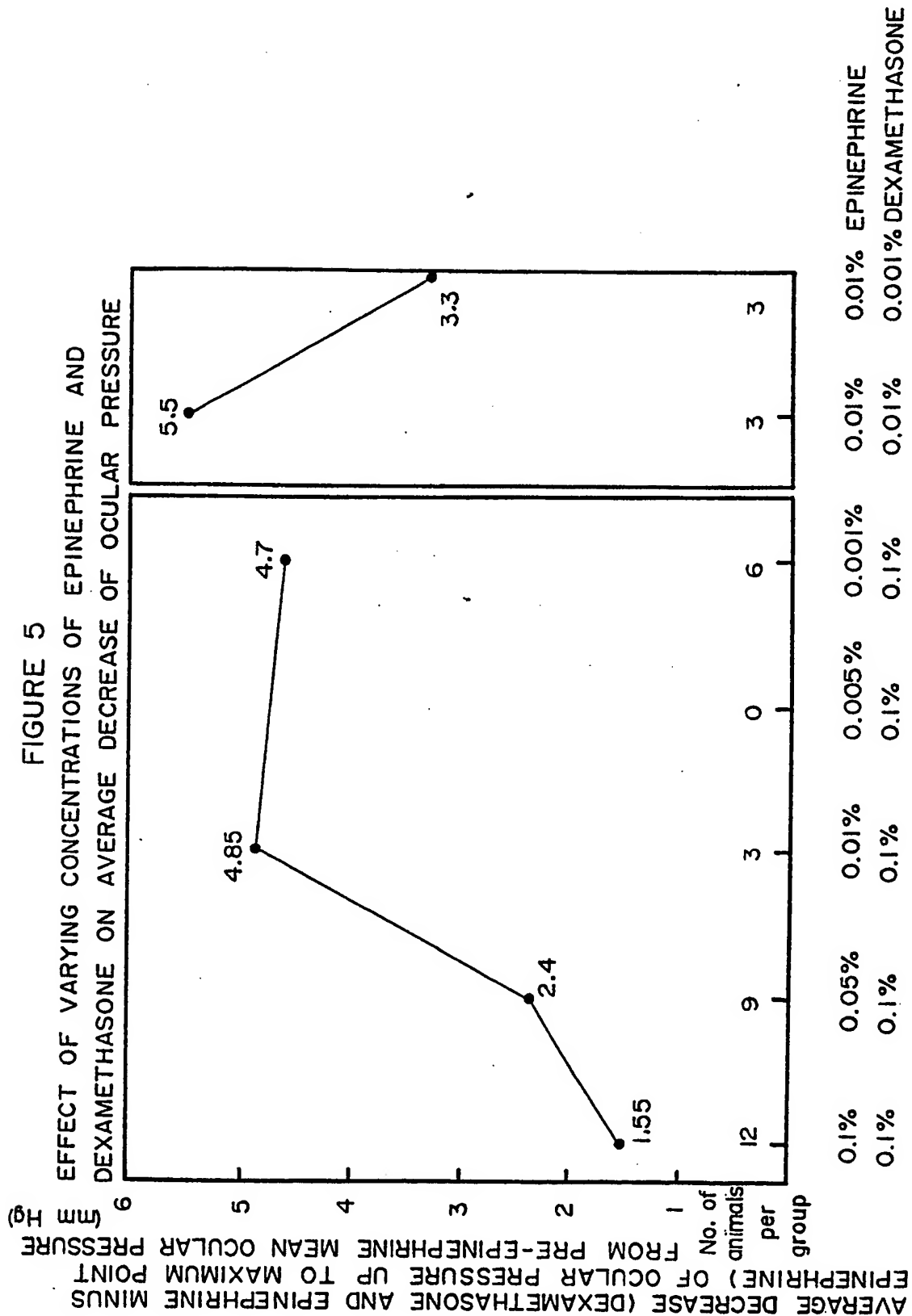
DOSE RESPONSE TO EPINEPHRINE BITARTRATE  
DIFFERENCE IN MEAN IOP  
(EPINEPHRINE MINUS DEXAMETHASONE / EPINEPHRINE)  
AT 45 MINUTES AFTER TREATMENT WITH EPINEPHRINE



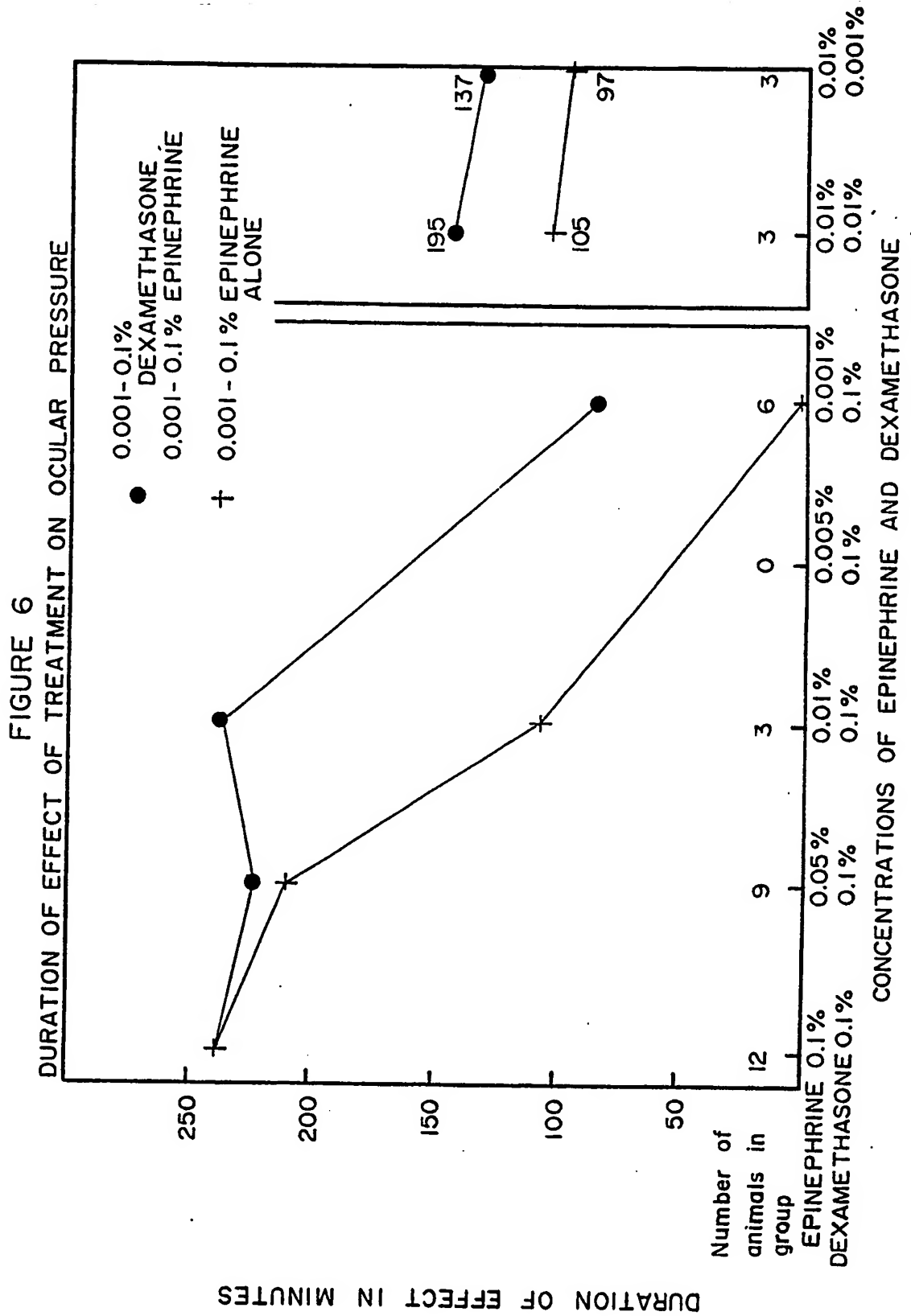
4/6

FIGURE 4  
DOSE - RESPONSE CURVE : 0.1% DEXAMETHASONE  
0.001- 0.1% EPINEPHRINE





6/6



# INTERNATIONAL SEARCH REPORT

International Application No **PCT/US86/01862**

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>3</sup> According to International Patent Classification (IPC) or to both National Classification and IPC IPC(4): <b>A61K 31/56,</b> U.S. CL: <b>514/171, 514/179; 514/180, 514/913</b>																				
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; margin-top: 10px;">Minimum Documentation Searched <sup>4</sup></div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%;">Classification System</th> <th style="width: 80%;">Classification Symbols</th> </tr> <tr> <td style="text-align: center; padding: 5px;"><b>U.S.</b></td> <td style="padding: 5px;"><b>514/171; 514/179; 514/180; 415/913</b></td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>5</sup></div> <p style="margin-top: 10px;"><b>Cas-on-line: Corticosteroid; adrenergic; glaucoma; ophthalm? intraocular; eye</b></p>			Classification System	Classification Symbols	<b>U.S.</b>	<b>514/171; 514/179; 514/180; 415/913</b>														
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<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>14</sup> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%;">Category <sup>*</sup></th> <th style="width: 60%;">Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup></th> <th style="width: 30%;">Relevant to Claim No. <sup>18</sup></th> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>A</b></td> <td style="padding: 5px;"><b>Martindale- The Extra Pharmacopoeia, edition 28, published 1982, (London, England), The Pharmaceutical Press, See page 447, column 2.</b></td> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>1-13</b></td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>X</b></td> <td style="padding: 5px;"><b>US,A, 3,320,125 (GRIM) 16 May 1967, See column 1, lines 11-13 and Claim 1.</b></td> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>9-13</b></td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>X</b></td> <td style="padding: 5px;"><b>US,A, 2,801,202 (POETSCH) 30 July 1957, See column 1, lines 20-45.</b></td> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>9-13</b></td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>A</b></td> <td style="padding: 5px;"><b>US,A, 4,271,143 (SCHOENWALD) 2 June 1981, See entire document.</b></td> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>1-13</b></td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>A</b></td> <td style="padding: 5px;"><b>US,A, 4,255,415 (CHRAI) 10 March 1981, See entire document.</b></td> <td style="text-align: center; vertical-align: top; padding: 5px;"><b>1-13</b></td> </tr> </table>			Category <sup>*</sup>	Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>	<b>A</b>	<b>Martindale- The Extra Pharmacopoeia, edition 28, published 1982, (London, England), The Pharmaceutical Press, See page 447, column 2.</b>	<b>1-13</b>	<b>X</b>	<b>US,A, 3,320,125 (GRIM) 16 May 1967, See column 1, lines 11-13 and Claim 1.</b>	<b>9-13</b>	<b>X</b>	<b>US,A, 2,801,202 (POETSCH) 30 July 1957, See column 1, lines 20-45.</b>	<b>9-13</b>	<b>A</b>	<b>US,A, 4,271,143 (SCHOENWALD) 2 June 1981, See entire document.</b>	<b>1-13</b>	<b>A</b>	<b>US,A, 4,255,415 (CHRAI) 10 March 1981, See entire document.</b>	<b>1-13</b>
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>*</sup> Special categories of cited documents: <sup>15</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art,</p> <p>"&amp;" document member of the same patent family</p> </div> </div>																				
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## III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, <sup>1a</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No <sup>18</sup>
X	GB,A, 755,156 (SMITH KLINE) 15 August 1956, See page 1, lines 38-42 and lines 85-95.	9-13
X	Invest. Ophthalmol. Vis. Sci. Volume 24, (suppl.), number 5, published 1983, (Harris) "Dexamethasone-induced Stimulat- ion of Beta-adrenergic Sensitive Adenylate Cyclase in Ciliary Process Epithelium", See entire abstract.	1-13
Y	Invest. Ophthalmol. Vis Sci. Volume 26, No. 3 (suppl.), published March 1985, (Ungricht), "Enhanced Ocular Hypotensive Response to Epinephrine with prior Dexamethasone Treatment". See entire abstract.	1-13
A	Ocular Pharmacology, edition no. 5, published 1983, (St. Louis, Missouri, USA), (Havener), see pages 275-290.	1-13
A	The Merck Manual of Diagnosis and Therapy, edition no. 14, published 1982 (Rahway, New Jersey, USA), Robert Berkow, "Airways Obstruction" see pages 615-616 and 625-627.	1-13

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